WE CLAIM:

1. A method comprising

(a) identifying a non-nucleotide prototype compound;

(b) substituting the prototype compound with a phosphonate-containing group to produce a candidate compound; and

(a) determining the anti-HIV activity of the candidate compound.

2. A method comprising

(a) selecting a non-nucleotide candidate compound containing at least one esterified carboxyl or esterified phosphonate-containing group; and

(b) determining the intracellular persistence of the candidate compound or a esterolytic metabolite of the esterified carboxyl or phosphonate-containing group thereof.

3. The method of claim 1 wherein the tissue selectivity of the candidate compound and/or at least one of its intracellular depot metabolites is determined.

4. The method of claim 1 wherein the intracellular residence time of said candidate compound and/or at least one of its intracellular depot metabolites is determined.

5. The method of claim 2 comprising additionally determining the activity of at least one of said metabolites against HIV protease.

6. The method of claim 2 wherein the metabolite is a carboxylic acid.

7. The method of claims 1 or 2 comprising determining the ability of the candidate to inhibit HIV.

8. The method of claim 1 wherein the prototype is already known to have therapeutic activity against HIV.

9. The method of claim 2 comprising selecting and determining the intracellular persistence of a plurality of candidate compounds.

10. The method of claims 1 or 2 wherein compounds which are not candidate compounds are tested in parallel together with at least one candidate compound.

11. The method of claim 2 comprising determining cleavage of one or more candidates by GS-7340 Ester Hydrolase.

12. The method of claims 1 or 2 wherein the candidate is an amino acid phosphonoamidate in which a carboxyl of the amino acid is esterified.

13. The method of claim 1 wherein the prototype compound is known to inhibit HIV protease, HIV integrase or HIV reverse transcriptase.

14. The method of claim 1 wherein the prototype compound is not known to be an analogue of a naturally occurring phosphate-containing enzyme substrate.

15. The method of claim 1 wherein the prototype compound is not a nucleoside.

16. The method of claim 1 wherein the prototype compound does not contain a nucleoside base.

17. The method of claim 1 wherein an intracellular depot metabolite is tested.

18. The method of claim 1 also comprising determining the resistance of HIV to the candidate compound and/or its intracellular depot metabolite.

19. The method of claim 1 comprising determining the tissue selectivity and/or intracellular residence time for a first candidate compound and/or its intracellular depot metabolite, preparing or selecting additional analogues of said first candidate compound, and determining the therapeutic activity of said additional analogues without determining tissue selectivity and/or intracellular residence time of said analogues.

20. The method of claim 1 comprising determining the safety and/or anti-HIV therapeutic activity of the candidate compound in *in vitro* cell culture, in enzyme assay, in animals or in humans.

21. The method of claim 1 wherein the prototype compound is a pharmaceutical product licensed by the US Food and Drug Administration.

22. The method of claim 1 wherein the prototype compound is one which is disclosed to have anti-HIV activity.in a patent or published patent application on or before the filing date of this application.

23. The method of claim 1 comprising determining susceptibility to hydrolysis of the carboxyl or phosphonate esters by GS-7340 Ester Hydrolase, said Hydrolase characterized by being capable of being recovered from human PBMCs by a process comprising

(b) lysing human PBMCs;

(c) extracting the lysed cells with detergent;

(d) separating the solids from supernatant and recovering the supernatant;

(e) contacting the supernatant with an anion exchange medium;

(f) eluting the Hydrolase from the anion exchange medium;

(g) contacting the eluate with a hydrophobic chromatographic medium; and

(h) eluting the Hydrolase from the hydrophobic chromatographic medium.

24. The method of claim 23 wherein the Hydrolase has a MW on gel filtration chromatography of about 70-100 kDa, has a pI of about 4.5-5.5 by chromatofocusing, is inhibited by 3,4 dichloroisocoumarin, binds to Butyl Sepharose HIC, binds to anion exchange medium Q15, and is capable of being recovered from human PBMCs.

25. The method of claim 2 wherein the intracellular residence time is determined as the half-life of at least one intracellular depot metabolite within a lymphoid tissue.

26. The method of claim 25 wherein the lymphoid tissue is PBMCs, helper cells, killer cells or lymph nodes.

27. The method of claim 1 wherein determining anti-HIV activity is by *in vitro* assay.

28. The method of claim 27 wherein the assay is conducted in an animal model or clinical trials

29. The method of claims 1 or 2 comprising the additional steps of identifying a clinical trial compound from the final step, entering into clinical trials with said clinical trial compound, obtaining regulatory approval to market said clinical trial compound for the treatment of HIV, and selling said clinical trial compound after said regulatory approval.

30. The method of claim 29 wherein the clinical trial compound is not identical to the candidate compound

31. The method of claim 2 wherein intracellular persistence was determined by clinical studies comprising determination of the amount and timing of dosing of the candidate compound.

32. The method of claim 2 wherein the metabolite is intracellularly sequestered in PBMCs.

33. The method of claim 2 wherein greater than one metabolite is tested to determine intracellular residence time.

34. The method of claim 2 wherein the intracellular persistence is determined in PBMCs.

35. The method of claim 2 wherein the metabolite comprises the phosphonate group of Metabolite X.

36. The method of claim 2 wherein the metabolite comprises an unesterified carboxyl group.

37. The method of claim 2 wherein the intracellular depot metabolite comprises the group -P(O)(OH)-.

38. A library of candidate non-nucleotide anti-HIV compounds comprising a plurality of candidate compounds suspected to have anti HIV activity which contain esterified carboxyl or esterified phosphonate groups.

39. A library of candidate anti-HIV compounds which does not consist solely of nucleotides and which comprises a plurality of candidate compounds suspected to have anti-HIV activity which contain esterified carboxyl or esterified phosphonate groups.

40. The library of claims 38 or 39 comprising at least about 10 candidate compounds.

41. The library of claims 38 or 39 wherein the candidate compounds comprise (a) a phosphonate substituted with an amino acid or an organic acid, or (b) an amino acid, at least one of the carboxyl groups of the amino acid or organic acid being esterified.

42. The library of claims 38 or 39 wherein the compounds in the library are stored in discrete containers.

43. A method comprising testing the library of claims 39, 40, 41, or 42 to determine the anti-HIV activity of at least one candidate compound in the library.

44. The method of claim 43 comprising determining for tissue selectivity and/or the intracellular persistence of at least one of said candidate compounds and/or at least one of their intracellular metabolites.

45. The method of claim 43 comprising the additional steps of identifying a clinical trial compound from said library, entering into clinical trials with said clinical trial compound, obtaining regulatory approval to market said clinical trial compound for the treatment of HIV, and selling said clinical trial compound after said regulatory approval.

46. Isolated GS-7340 Ester Hydrolase.

47. The Hydrolase of claim 46 which is purified to a single major band on gel filtration chromatography.

48. The Hydrolase of claim 46 which is capable of being recovered from human PBMC cells.

49. The Hydrolase of claim 48 wherein the Hydrolase has a MW on gel filtration chromatography of about 70-100 kDa.

50. The Hydrolase of claim 50 which has a pI of about 4.5-5.5 by chromatofocusing

51. The Hydrolase of claim 50 which is inhibited by 3,4 dichloroisocoumarin,

52. The Hydrolase of claim 51 which binds to Butyl Sepharose HIC.

53. The Hydrolase of claim 52 which binds to anion exchange medium Q15.

54. The Hydrolase of claim 53 which binds to hydroxyapatite.

55. The Hydrolase of claim 46 which is cross-linked to an insoluble medium.

56. A method comprising obtaining a substantially pure organic molecule, optionally contacting the organic molecule with another molecule to produce a composition, and contacting the Hydrolase of claim 46 with said organic molecule or composition.

57. The method of claim 56 wherein the organic molecule is an anti-HIV compound.

58. A method comprising contacting GS-7340 Ester Hydrolase with an organic compound in an *in vitro* or cell culture environment.

59. The method of claim 58 wherein the environment is cell free.

60. A composition comprising a substantially pure organic compound and isolated GS-7340 Ester Hydrolase.

61. A composition comprising an organic compound and GS-7340 Ester Hydrolase in an *in vitro* or cell culture environment.

62. In a method for identifying an anti-HIV therapeutic compound, the improvement comprising substituting a prototype compound with an esterified phosphonate or esterified carboxyl group to produce a candidate compound and assaying the resulting candidate compound for its anti-HIV activity.

63. The method of claim 61 wherein the candidate is assayed for its intracellular persistence.

64. The method of claim 63 wherein the candidate is assayed for its extracellular stability against hydrolysis of the carboxyl or phosphonate ester.

65. The method of claim 64 comprising selecting from a plurality of candidates a candidate which is esterolytically cleaved intracellularly to yield an intracellular persistent metabolite having anti-HIV activity and which candidate is substantially esterolytically stable against extracellular hydrolysis of the carboxyl or phosphonate ester.

66. The method of claim 65 wherein the candidate is substantially stable against hydrolysis of the carboxyl or phosphonate esters outside of

67. The method of claim 62 wherein the candidate is substituted with a phosphonate group comprising monosubstitution with (a) an amino acid linked through an amino group to the phosphorus atom or (b) an organic acid, and wherein a carboxylic acid of the amino acid or organic acid is esterified.

68. The method of claim 62 wherein the candidate is substituted with a group comprising an amino acid, wherein a carboxylic acid of the amino acid is esterified.

69. The method of claim 68 wherein the carboxylic acid is the residue of a hydroxyorganic acid linked to the phosphorus atom through an oxygen atom.

70. The method of claims 68 or 69 wherein the hydroxy group of the hydroxyorganic acid or the amino group of the amino acid are in the alpha position.

71. A method for identifying a candidate compound as a suitable pro-drug, comprising:

(a) providing the candidate compound having an esterified phosphonate group or an esterified carboxyl group;

(b) contacting the candidate compound with an extract capable of catalyzing the hydrolysis of a carboxylic ester; and

(c) identifying the candidate compound as a suitable pro-drug if the metabolite compound has a phosphonic acid group instead of the esterified phosphonate group of the candidate compound, or a carboxylic acid group instead of the esterified carboxyl group of the candidate compound.

72. The method of claim 71, wherein said extract is obtained from peripheral blood mononuclear cells.

73. A method for identifying a candidate compound as a suitable pro-drug, comprising:

(a) providing the candidate compound having an esterified phosphonate group or an esterified carboxyl group;

(b) contacting the candidate compound with an extract of peripheral blood mononuclear cells having carboxylic ester hydrolase activity to produce a metabolite compound; and

(c) identifying the candidate compound as a suitable pro-drug if the metabolite compound has a phosphonic acid group instead of the esterified phosphonate group of the candidate compound, or a carboxylic acid group instead of the esterified carboxyl group of the candidate compound.

74. The method of claim 73, wherein said providing step comprises providing a candidate compound formed by substituting a prototype compound known to have anti-HIV therapeutic activity with an esterified phosphonate or carboxyl group.

75. The method of claim 74, wherein said prototype compound is not a nucleoside, and does not contain a nucleoside base.

76. The method of claim 73, wherein said providing step comprises providing a candidate compound that is an amino acid phosphonoamidate, wherein a carboxyl group of the amino acid is esterified.

77. The method of claim 73, wherein said providing step comprises providing a candidate compound that is substantially stable against extracellular hydrolysis of the esterified group.

78. The method of claim 73, wherein said providing step comprises providing a candidate compound formed by substituting a prototype compound.

79. The method of claim 73, further comprising (d) determining the intracellular persistence of the candidate compound.

80. The method of claim 73, further comprising (d) determining the intracellular persistence of the metabolite compound.

81. The method of claim 73, further comprising (d) determining the intracellular persistence of the candidate compound and the metabolite compound.

82. The method of claim 73, further comprising (d) determining the tissue selectivity of the candidate compound.

83. The method of claim 73, further comprising (d) determining the tissue selectivity of the metabolite compound.

84. The method of claim 73, further comprising (d) determining the tissue selectivity of the candidate compound and the metabolite compound.

85. The method of claim 73, further comprising (d) determining the anti-HIV protease activity of the metabolite compound.

86. The method of claim 73, further comprising (d) determining the HIV-inhibition ability of the candidate compound.

87. The method of claim 73, further comprising (d) determining the resistance of HIV to the candidate compound.

88. The method of claim 73, further comprising (d) determining the resistance of HIV to the metabolite compound.

89. The method of claim 73, further comprising (d) determining the resistance of HIV to the candidate compound and the metabolite compound.

90. The method of claim 73, further comprising (d) determining the intracellular residence time of the candidate compound.

91. The method of claim 73, further comprising (d) determining the intracellular residence time of the metabolite compound.

92. The method of claim 73, further comprising (d) determining the intracellular residence time of the candidate compound and the metabolite compound.

93. The method of claim 90, wherein said step of determining the intracellular residence time of the metabolite compound comprises determining the half-life of the metabolite compound within lymphoid tissue.

94. The method of claim 91, wherein said step of determining the intracellular residence time of the metabolite compound comprises determining the half-life of the metabolite compound within lymphoid tissue.

95. The method of claim 92, wherein said step of determining the intracellular residence time of the metabolite compound comprises determining the half-life of the metabolite compound within lymphoid tissue.

96. The method of claim 93, wherein said step of determining the half-life of the metabolite compound further comprises determining the half-life of the metabolite compound within helper cells, killer cells, lymph nodes, or peripheral blood mononuclear cells.

97. The method of claim 94, wherein said step of determining the half-life of the metabolite compound further comprises determining the half-life of the metabolite compound within helper cells, killer cells, lymph nodes, or peripheral blood mononuclear cells.

98. The method of claim 95, wherein said step of determining the half-life of the metabolite compound further comprises determining the half-life of the metabolite compound within helper cells, killer cells, lymph nodes, or peripheral blood mononuclear cells.

99. The method of claim 73, wherein said contacting step comprises contacting the candidate compound with GS-7340 Ester Hydrolase in a cell-free environment.

100. The method of claim 73, wherein said contacting step comprises contacting the candidate compound with GS-7340 Ester Hydrolase in vitro.

101. The method of claim 73, wherein said contacting step comprises contacting the candidate compound with GS-7340 Ester Hydrolase in cell culture.

102. The method of claim 101, wherein said contacting step comprises contacting the candidate compound with GS-7340 Ester Hydrolase in a culture of peripheral blood mononuclear cells.

103. A method for identifying a candidate compound as a suitable pro-drug, comprising:

(a) providing the candidate compound having an esterified phosphonate group;

(b) contacting the candidate compound with GS-7340 Ester Hydrolase to produce a metabolite compound; and

(c) identifying the candidate compound as a suitable pro-drug if the metabolite compound has a phosphonic acid group instead of the esterified phosphonate group of the candidate compound.

104. The method of claim 103, wherein said providing step further comprises monosubstitution of the esterified phosphonate group with an organic acid having an esterified carboxyl group.

105. The method of claim 103, wherein said providing step further comprises monosubstitution of the esterified phosphonate group with an amino acid linked through an amino group to the phosphorus atom, wherein the amino acid has an esterified carboxyl group.

106. The method of claim 103, wherein said providing step comprises providing a candidate compound formed by substituting a prototype compound known to have anti-HIV therapeutic activity with an esterified phosphonate or carboxyl group.

107. The method of claim 106, wherein said prototype compound is not a nucleoside, and does not contain a nucleoside base.

108. The method of claim 103, wherein said providing step comprises providing a candidate compound that is an amino acid phosphonoamidate, wherein a carboxyl group of the amino acid is esterified.

109. The method of claim 103, wherein said providing step comprises providing a candidate compound that is substantially stable against extracellular hydrolysis of the esterified group.

110. The method of claim 103, wherein said providing step comprises providing a candidate compound formed by substituting a prototype compound

111. The method of claim 103, further comprising (d) determining the intracellular persistence of the candidate compound.

112. The method of claim 103, further comprising (d) determining the intracellular persistence of the metabolite compound.

113. The method of claim 103, further comprising (d) determining the intracellular persistence of the candidate compound and the metabolite compound.

114. The method of claim 103, further comprising (d) determining the tissue selectivity of the candidate compound.

115. The method of claim 103, further comprising (d) determining the tissue selectivity of the metabolite compound.

116. The method of claim 103, further comprising (d) determining the tissue selectivity of the candidate compound and the metabolite compound.

117. The method of claim 103, further comprising (d) determining the anti-HIV protease activity of the metabolite compound.

118. The method of claim 103, further comprising (d) determining the HIV-inhibition ability of the candidate compound.

119. The method of claim 103, further comprising (d) determining the resistance of HIV to the candidate compound.

120. The method of claim 103, further comprising (d) determining the resistance of HIV to the metabolite compound.

121. The method of claim 103, further comprising (d) determining the resistance of HIV to the candidate compound and the metabolite compound.

122. The method of claim 103, further comprising (d) determining the intracellular residence time of the candidate compound.

123. The method of claim 103, further comprising (d) determining the intracellular residence time of the metabolite compound.

124. The method of claim 103, further comprising (d) determining the intracellular residence time of the candidate compound and the metabolite compound.

125. The method of claim 122, wherein said step of determining the intracellular residence time of the metabolite compound comprises determining the half-life of the metabolite compound within lymphoid tissue

126. The method of claim 123, wherein said step of determining the intracellular residence time of the metabolite compound comprises determining the half-life of the metabolite compound within lymphoid tissue.

127. The method of claim 124, wherein said step of determining the intracellular residence time of the metabolite compound comprises determining the half-life of the metabolite compound within lymphoid tissue.

128. The method of claim 125, wherein said step of determining the half-life of the metabolite compound further comprises determining the half-life of the metabolite compound within helper cells, killer cells, lymph nodes, or peripheral blood mononuclear cells.

129. The method of claim 126, wherein said step of determining the half-life of the metabolite compound further comprises determining the half-life of the metabolite compound within helper cells, killer cells, lymph nodes, or peripheral blood mononuclear cells.

130. The method of claim 127, wherein said step of determining the half-life of the metabolite compound further comprises determining the half-life of the metabolite compound within helper cells, killer cells, lymph nodes, or peripheral blood mononuclear cells.

131. The method of claim 103, wherein said contacting step comprises contacting the candidate compound with GS-7340 Ester Hydrolase in a cell-free environment.

132. The method of claim 103, wherein said contacting step comprises contacting the candidate compound with GS-7340 Ester Hydrolase in vitro.

133. The method of claim 103, wherein said contacting step comprises contacting the candidate compound with GS-7340 Ester Hydrolase in cell culture.

134. The method of claim 133, wherein said contacting step comprises contacting the candidate compound with GS-7340 Ester Hydrolase in a culture of peripheral blood mononuclear cells.

135. A method for identifying a candidate compound as a suitable pro-drug, comprising:

(a) providing the candidate compound having an esterified carboxyl group;

(b) contacting the candidate compound with GS-7340 Ester Hydrolase to produce an metabolite compound; and

(c) identifying the candidate compound as a suitable pro-drug if the metabolite compound has a carboxylic acid group instead of the esterified carboxyl group of the candidate compound.

136. The method of claim 135, wherein said providing step comprises providing a candidate compound substituted with an amino acid group, wherein the amino acid has an esterified carboxyl group.

137. The method of claim 135, wherein said providing step comprises providing a candidate compound formed by substituting a prototype compound known to have anti-HIV therapeutic activity with an esterified phosphonate or carboxyl group.

138. The method of claim 137, wherein said prototype compound is not a nucleoside, and does not contain a nucleoside base.

139. The method of claim 135, wherein said providing step comprises providing a candidate compound that is an amino acid phosphonoamidate, wherein a carboxyl group of the amino acid is esterified.

140. The method of claim 135, wherein said providing step comprises providing a candidate compound that is substantially stable against extracellular hydrolysis of the esterified group.

141. The method of claim 135, wherein said providing step comprises providing a candidate compound formed by substituting a prototype compound

142. The method of claim 135, further comprising (d) determining the intracellular persistence of the candidate compound.

143. The method of claim 135, further comprising (d) determining the intracellular persistence of the metabolite compound.

144. The method of claim 135, further comprising (d) determining the intracellular persistence of the candidate compound and the metabolite compound.

145. The method of claim 135, further comprising (d) determining the tissue selectivity of the candidate compound.

146. The method of claim 135, further comprising (d) determining the tissue selectivity of the metabolite compound.

147. The method of claim 135, further comprising (d) determining the tissue selectivity of the candidate compound and the metabolite compound.

148. The method of claim 135, further comprising (d) determining the anti-HIV protease activity of the metabolite compound.

149. The method of claim 135, further comprising (d) determining the HIV-inhibition ability of the candidate compound.

150. The method of claim 135, further comprising (d) determining the resistance of HIV to the candidate compound.

151. The method of claim 135, further comprising (d) determining the resistance of HIV to the metabolite compound.

152. The method of claim 135, further comprising (d) determining the resistance of HIV to the candidate compound and the metabolite compound.

153. The method of claim 135, further comprising (d) determining the intracellular residence time of the candidate compound.

154. The method of claim 135, further comprising (d) determining the intracellular residence time of the metabolite compound.

155. The method of claim 135, further comprising (d) determining the intracellular residence time of the candidate compound and the metabolite compound.

156. The method of claim 153, wherein said step of determining the intracellular residence time of the metabolite compound comprises determining the half-life of the metabolite compound within lymphoid tissue.

157. The method of claim 154, wherein said step of determining the intracellular residence time of the metabolite compound comprises determining the half-life of the metabolite compound within lymphoid tissue.

158. The method of claim 155, wherein said step of determining the intracellular residence time of the metabolite compound comprises determining the half-life of the metabolite compound within lymphoid tissue.

159. The method of claim 156, wherein said step of determining the half-life of the metabolite compound further comprises determining the half-life of the metabolite compound within helper cells, killer cells, lymph nodes, or peripheral blood mononuclear cells.

160. The method of claim 157, wherein said step of determining the half-life of the metabolite compound further comprises determining the half-life of the metabolite compound within helper cells, killer cells, lymph nodes, or peripheral blood mononuclear cells.

161. The method of claim 158, wherein said step of determining the half-life of the metabolite compound further comprises determining the half-life of the metabolite compound within helper cells, killer cells, lymph nodes, or peripheral blood mononuclear cells.

162. The method of claim 135, wherein said contacting step comprises contacting the candidate compound with GS-7340 Ester Hydrolase in a cell-free environment.

163. The method of claim 135, wherein said contacting step comprises contacting the candidate compound with GS-7340 Ester Hydrolase in vitro.

164. The method of claim 135, wherein said contacting step comprises contacting the candidate compound with GS-7340 Ester Hydrolase in cell culture.

165. The method of claim 164, wherein said contacting step comprises contacting the candidate compound with GS-7340 Ester Hydrolase in a culture of peripheral blood mononuclear cells.

166. A method for identifying a candidate compound as a suitable pro-drug, comprising:

(a) providing the candidate compound having an esterified phosphonate group or an esterified carboxyl group;

(b) contacting the candidate compound with an extract of peripheral blood mononuclear cells which has carboxylic ester hydrolase activity but does not cleave alpha-napthyl acetate, to produce a metabolite compound; and

(c) identifying the candidate compound as a suitable pro-drug if the metabolite compound has a phosphonic acid group instead of the esterified phosphonate group of the candidate compound, or a carboxylic acid group instead of the esterified carboxyl group of the candidate compound.

167. The method of claim 166, wherein said providing step comprises providing a candidate compound formed by substituting a prototype compound known to have anti-HIV therapeutic activity with an esterified phosphonate or carboxyl group.

168. The method of claim 167, wherein said prototype compound is not a nucleoside, and does not contain a nucleoside base.

169. The method of claim 166, wherein said providing step comprises providing a candidate compound that is an amino acid phosphonoamidate, wherein a carboxyl group of the amino acid is esterified.

170. The method of claim 166, wherein said providing step comprises providing a candidate compound that is substantially stable against extracellular hydrolysis of the esterified group.

171. The method of claim 166, wherein said providing step comprises providing a candidate compound formed by substituting a prototype compound

172. The method of claim 166, further comprising (d) determining the intracellular persistence of the candidate compound.

173. The method of claim 166, further comprising (d) determining the intracellular persistence of the metabolite compound.

174. The method of claim 166, further comprising (d) determining the intracellular persistence of the candidate compound and the metabolite compound.

175. The method of claim 166, further comprising (d) determining the tissue selectivity of the candidate compound.

176. The method of claim 166, further comprising (d) determining the tissue selectivity of the metabolite compound.

177. The method of claim 166, further comprising (d) determining the tissue selectivity of the candidate compound and the metabolite compound.

178. The method of claim 166, further comprising (d) determining the anti-HIV protease activity of the metabolite compound.

179. The method of claim 166, further comprising (d) determining the HIV-inhibition ability of the candidate compound.

180. The method of claim 166, further comprising (d) determining the resistance of HIV to the candidate compound.

181. The method of claim 166, further comprising (d) determining the resistance of HIV to the metabolite compound.

182. The method of claim 166, further comprising (d) determining the resistance of HIV to the candidate compound and the metabolite compound.

183. The method of claim 166, further comprising (d) determining the intracellular residence time of the candidate compound.

184. The method of claim 166, further comprising (d) determining the intracellular residence time of the metabolite compound.

185. The method of claim 166, further comprising (d) determining the intracellular residence time of the candidate compound and the metabolite compound.

186. The method of claim 183, wherein said step of determining the intracellular residence time of the metabolite compound comprises determining the half-life of the metabolite compound within lymphoid tissue.

187. The method of claim 184, wherein said step of determining the intracellular residence time of the metabolite compound comprises determining the half-life of the metabolite compound within lymphoid tissue.

188. The method of claim 185, wherein said step of determining the intracellular residence time of the metabolite compound comprises determining the half-life of the metabolite compound within lymphoid tissue.

189. The method of claim 186, wherein said step of determining the half-life of the metabolite compound further comprises determining the half-life of the metabolite compound within helper cells, killer cells, lymph nodes, or peripheral blood mononuclear cells.

190. The method of claim 187, wherein said step of determining the half-life of the metabolite compound further comprises determining the half-life of the metabolite compound within helper cells, killer cells, lymph nodes, or peripheral blood mononuclear cells.

191. The method of claim 188, wherein said step of determining the half-life of the metabolite compound further comprises determining the half-life of the metabolite compound within helper cells, killer cells, lymph nodes, or peripheral blood mononuclear cells.

192. The method of claim 166, wherein said contacting step comprises contacting the candidate compound with GS-7340 Ester Hydrolase in a cell-free environment.

193. The method of claim 166, wherein said contacting step comprises contacting the candidate compound with GS-7340 Ester Hydrolase in vitro.

194. The method of claim 166, wherein said contacting step comprises contacting the candidate compound with GS-7340 Ester Hydrolase in cell culture.

195. The method of claim 194, wherein said contacting step comprises contacting the candidate compound with GS-7340 Ester Hydrolase in a culture of peripheral blood mononuclear cells.

196. A candidate compound identified by the method of claim 71, wherein the candidate compound is an amino acid phosphonoamidate in which a carboxyl group of the amino acid is esterified.

197. A candidate compound identified by the method of claim 103, wherein the candidate compound is an amino acid phosphonoamidate in which a carboxyl group of the amino acid is esterified.

198. A candidate compound identified by the method of claim 134, wherein the candidate compound is an amino acid phosphonoamidate in which a carboxyl group of the amino acid is esterified.

199. A candidate compound identified by the method of claim 164, wherein the candidate compound is an amino acid phosphonoamidate in which a carboxyl group of the amino acid is esterified.

200. A candidate compound identified by the method of claim 71, wherein the candidate compound is substituted with an amino acid group in which a carboxyl group of the amino acid is esterified.

201. A candidate compound identified by the method of claim 103, wherein the candidate compound is substituted with an amino acid group in which a carboxyl group of the amino acid is esterified.

202. A candidate compound identified by the method of claim 134, wherein the candidate compound is substituted with an amino acid group in which a carboxyl group of the amino acid is esterified.

203. A candidate compound identified by the method of claim 164, wherein the candidate compound is substituted with an amino acid group in which a carboxyl group of the amino acid is esterified.

204. The candidate compound of claim 200, wherein the amino group of the amino acid is in the alpha position.

205. The candidate compound of claim 201, wherein the amino group of the amino acid is in the alpha position.

206. The candidate compound of claim 202, wherein the amino group of the amino acid is in the alpha position.

207. The candidate compound of claim 203, wherein the amino group of the amino acid is in the alpha position.

208. A candidate compound identified by the method of claim 71, wherein the esterified phosphonate group is monosubstituted with a hydroxyorganic acid linked to the phosphorus atom through an oxygen atom.

209. The candidate compound of claim 133, wherein the hydroxy group of the hydroxyorganic acid is in the alpha position.

210. A candidate compound identified by the method of claim 71, wherein the candidate compound is substantially stable against extracellular hydrolysis of the esterified group.

211. A candidate compound identified by the method of claim 103, wherein the candidate compound is substantially stable against extracellular hydrolysis of the esterified group.

212. A candidate compound identified by the method of claim 134, wherein the candidate compound is substantially stable against extracellular hydrolysis of the esterified group.

213. A candidate compound identified by the method of claim 164, wherein the candidate compound is substantially stable against extracellular hydrolysis of the esterified group.

214. A method of screening candidate compounds for suitability as anti-HIV therapeutic agents, comprising:

(a) providing a candidate compound identified by the method of claim 71;

(b) determining the anti-HIV activity of the candidate compound; and

(c) determining the intracellular persistence of the candidate compound.

215. A method of screening candidate compounds for suitability as anti-HIV therapeutic agents, comprising:

(a) providing a candidate compound identified by the method of claim 103;

(b) determining the anti-HIV activity of the candidate compound; and

(c) determining the intracellular persistence of the candidate compound.

216. A method of screening candidate compounds for suitability as anti-HIV therapeutic agents, comprising:

(a) providing a candidate compound identified by the method of claim 134;

(b) determining the anti-HIV activity of the candidate compound; and

(c) determining the intracellular persistence of the candidate compound.

217. A method of screening candidate compounds for suitability as anti-HIV therapeutic agents, comprising:

(a) providing a candidate compound identified by the method of claim 164;

(b) determining the anti-HIV activity of the candidate compound; and

(c) determining the intracellular persistence of the candidate compound.

218. The method of claim 214, wherein said step (b) comprises determining the activity of the candidate compound against HIV protease.

219. The method of claim 215, wherein said step (b) comprises determining the activity of the candidate compound against HIV protease.

220. The method of claim 216, wherein said step (b) comprises determining the activity of the candidate compound against HIV protease.

221. The method of claim 217, wherein said step (b) comprises determining the activity of the candidate compound against HIV protease.

222. The method of claim 214, wherein said step (b) comprises determining the ability of the candidate compound to inhibit HIV.

223. The method of claim 215, wherein said step (b) comprises determining the ability of the candidate compound to inhibit HIV.

224. The method of claim 216, wherein said step (b) comprises determining the ability of the candidate compound to inhibit HIV.

225. The method of claim 217, wherein said step (b) comprises determining the ability of the candidate compound to inhibit HIV.

226. The method of claim 222, wherein said step (b) comprises determining the ability of the candidate compound to inhibit HIV protease.

227. The method of claim 223, wherein said step (b) comprises determining the ability of the candidate compound to inhibit HIV protease.

228. The method of claim 224, wherein said step (b) comprises determining the ability of the candidate compound to inhibit HIV protease.

229. The method of claim 225, wherein said step (b) comprises determining the ability of the candidate compound to inhibit HIV protease.

230. The method of claim 222, wherein said step (b) comprises determining the ability of the candidate compound to inhibit HIV integrase.

231. The method of claim 223, wherein said step (b) comprises determining the ability of the candidate compound to inhibit HIV integrase.

232. The method of claim 224, wherein said step (b) comprises determining the ability of the candidate compound to inhibit HIV integrase.

233. The method of claim 225, wherein said step (b) comprises determining the ability of the candidate compound to inhibit HIV integrase.

234. The method of claim 222, wherein said step (b) comprises determining the ability of the candidate compound to inhibit HIV reverse transcriptase.

235. The method of claim 223, wherein said step (b) comprises determining the ability of the candidate compound to inhibit HIV reverse transcriptase.

236. The method of claim 224, wherein said step (b) comprises determining the ability of the candidate compound to inhibit HIV reverse transcriptase.

237. The method of claim 225, wherein said step (b) comprises determining the ability of the candidate compound to inhibit HIV reverse transcriptase.

238. The method of claim 214, wherein said step (b) further comprises determining the resistance of HIV to the candidate compound.

239. The method of claim 214, wherein said step (b) is performed by *in vitro* assay.

240. The method of claim 214, wherein said step (b) further comprises determining the anti-HIV activity of an acid metabolite of the candidate compound.

241. The method of claim 240, wherein said acid metabolite is a carboxylic acid compound formed by esterolytic hydrolysis of the candidate compound.

242. The method of claim 240, wherein said acid metabolite is a phosphonic acid compound formed by esterolytic hydrolysis of the candidate compound.

243. The method of claim 214, wherein said step (c) comprises determining the intracellular residence time of the candidate compound.

244. The method of claim 214, wherein said step (c) further comprises determining the intracellular residence time of an acid metabolite of the candidate compound.

245. The method of claim 244, wherein said acid metabolite is a carboxylic acid compound formed by esterolytic hydrolysis of the candidate compound.

246. The method of claim 244, wherein said acid metabolite is a phosphonic acid compound formed by esterolytic hydrolysis of the candidate compound.

247. The method of claim 244, wherein said step (c) further comprises determining the half-life of the metabolite compound within lymphoid tissue.

248. The method of claim 247, wherein in said step of determining the half-life of the metabolite compound within lymphoid tissue, the lymphoid tissue is selected from the group consisting of helper cells, killer cells, lymph nodes, and peripheral blood mononuclear cells.

249. The method of claim 214, further comprising (d) determining the tissue selectivity of the candidate compound.

250. The method of claim 249, wherein said step (d) further comprises determining the tissue selectivity of an acid metabolite of the candidate compound.